Metalation of Alkynes. 1. Effect of Alkyne Structure on the Rate of Acetoxymercuration[1,2]

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Received February 26, 1986

The rates of $Hg(OAc)_2$ addition to symmetrically and unsymmetrically substituted alkynes (4-octyne, 2-heptyne, 2-nonyne, 1,4-dimethoxy-2-butyne, 1,4-diacetoxy-2-butyne, methyl 2-octynoate, 1-phenylpropyne, 1-phenyl-1-pentyne, methyl 3-phenylpropynoate, and diphenylethyne) were measured in acetic acid. Activation parameters were determined for representative substrates. The corresponding vinylacetoxymercury acetates were isolated under preparative conditions. The rate law was overall second order, first order in both alkyne and mercuric acetate. Alkylacetylenes are more reactive than phenylacetylenes, and the reaction rate is decreased by electron-withdrawing substituents. The data are the first kinetic evidence for an associative process characterized by the electrophilic attack of mercuric acetate to the triple bond.

The reaction of alkynes with mercuric salts has been widely used in the synthesis of enol acetates[3] and the acid-catalyzed hydration to ketones.[4,5] Vinyl mercurials have been assumed to be intermediates[5,6] in such reactions, but the mechanism has not been investigated with the same detail as the reaction of alkenes with mercuric salts.[6,7]

Recently, there has been a renewed interest in the regio- and stereochemistry of alkyne acetoxymercuration.[8-10] However, after early reports on reactions in acidic aqueous media[11] and in acetic acid,[12] kinetic studies have not been performed, although they are necessary for a quantitative rationale of the reaction mechanism.[7,10]

We have previously discussed the mechanistic pathways for the overall reaction of ethynylferrocene and ethynylbenzene with mercuric acetate, leading to the corresponding hydration products.[13] We now report on a kinetic investigation of the first step of the reaction between alkynes and the same mercurating reagent in acetic acid, that leads to vinylacetoxymercury acetates (eq 1).

$$RC{\equiv}CR' + Hg(OAc)_2 \xrightarrow{AcOH} RC(OAc){=}C(HgOAc)R' + RC(HgOAc){=}C(OAc)R' \quad (1)$$

Both aliphatic and aromatic alkynes with different structures were used, in order to understand the effect of gross structural changes on the alkyne reactivity.

Results and Discussion

The addition of mercuric acetate to alkynes in acetic acid occurs smoothly at room temperature. The corresponding acetoxymercury vinylacetates have been isolated and identified, with results identical with those reported in the literature, when available. Acetic acid was used as the solvent, since the regio- and stereochemistry of the reaction in this solvent has been recently well established.[8,9,14]

Kinetic experiments were performed under pseudo-first-order conditions, generally using an excess of the mercurating agent, by a variety of techniques (gas chromatography, stopped-flow and conventional spectrophotometry), either following the disappearance of the alkyne or the formation of the addition product. When different methods were used with the same substrate, the results are in excellent agreement.

The reaction was generally followed up to 80-90% conversion. When the occurrence of the subsequent protodemetalation reaction became significant, the rate constants were determined from data corresponding to 50-70% of the addition reaction (see Experimental Section).

The acetoxymercuration of alkynes follows a second-order rate law, first order in substrate and first order in the mercurating agent. The results are summarized in Table I.

Terminal alkynes were not investigated because of the concurrent reaction involving the acetylenic proton which leads to the insoluble bis(alkylacetylido)mercury derivatives.[13,15]

The high reactivity and the small spectral change associated with the reaction of dialkyl-substituted acetylenes made it necessary to work near the limits of the experimental methods. It was not possible to use a wide range of initial concentrations, but the obtained data are consistent and reproducible.

Alkylacetylenes were much more reactive than the aryl ones. Electron-withdrawing substituents (in particular, the methoxycarbonyl group) decreased the reactivity and also seemed to affect the reactivity of the triple bond independent of the other substituent. (See Table I, entries 6 and 9.) These results are the first kinetic evidence in support of the assumption that the electrophilic attack is the rate-determining step.[5]

Oxymercuration of carbon-carbon double bonds has been generally compared to bromination, since both are electrophilic additions likely to occur via a bridged cationic

(1) Dedicated to the memory of Professor Gabriello Illuminati (1922-1986), to whom we are deeply indebted for his teaching and guidance.
(2) Presented in part at the XII IUPAC Conference on Organometallic Chemistry.
(3) Hudrlick, P. F.; Hudrlick, A. M. *J. Org. Chem.* **1973**, *38*, 4254, and references therein.
(4) Rutledge, T. F. *Acetylenes and Allenes*; Reinhold: New York, 1969, and references therein.
(5) March, J. *Advanced Organic Chemistry. Reactions, Mechanisms, and Structure*, 3rd ed.; Wiley: New York, 1985.
(6) Schmid, G. H. In *The Chemistry of Carbon-Carbon Triple Bond*; Patai, Ed.; Wiley: New York, 1978; part 1.
(7) Fahey, R. C. In *Topics in Stereochemistry*; Eliel, E. L., Allinger, N. L., Eds., Interscience: New York, 1968; Vol. 3.
(8) Bach, R. D.; Woodard, R. A.; Anderson, T. J.; Glick, M. D. *J. Org. Chem.* **1982**, *47*, 3707.
(9) Uemura, S.; Miyoshi, H.; Okano, M. *J. Chem. Soc., Perkin Trans. 1*, **1980**, 1098.
(10) Spear, R. G.; Jensen, W. A. *Tetrahedron Lett.* **1977**, 4535.
(11) Frieman, R. H.; Kennedy, E. R.; Lucas, H. J. *J. Am. Chem. Soc.* **1937**, *59*, 722.
(12) Lemaire, H.; Lucas, H. J. *J. Am. Chem. Soc.* **1955**, *77*, 939.
(13) Bassetti, M.; Floris, B.; Illuminati, G. *Organometallics*, **1985**, *4*, 617.
(14) Drefahl, G.; Heublein, G.; Wintzer, A. *Angew. Chem.* **1958**, *70*, 166.
(15) Uemura, S.; Miyoshi, H.; Sohma, K.; Okano, M. *J. Chem. Soc., Chem. Commun.* **1975**, 548.

0022-3263/86/1951-4140$01.50/0

Table I. Overall Second-Order Rate Constants for the Acetoxymercuration of Alkynes at 25 °C

entry	alkyne	k_2, M^{-1} s^{-1}	$[Hg(OAc)_2]/[alkyne]$	method[a]
1	4-octyne	53 ± 10	11	C
		11.5 ± 1[b]	11	B
		21 ± 5[c]	11	B
2	2-heptyne	13.1 ± 1.5[b]	10	B
3	2-nonyne	11.7 ± 1[b]	10	B
4	1,4-dimethoxy-2-butyne	0.45 ± 0.02	12–29	B
5	1,4-diacetoxy-2-butyne	0.72 ± 0.04	13–17	B
6	methyl 2-octynoate	$(3.9 \pm 0.4) \times 10^{-4}$	24–30	B
7	1-phenylpropyne	$(2.3 \pm 0.4) \times 10^{-3}$	0.05–113	A, B
8	1-phenyl-1-pentyne	$(1.1 \pm 0.1) \times 10^{-3}$	12–13	B
9	methyl 3-phenylpropynoate	$(3.7 \pm 0.4) \times 10^{-4}$	37–71	B
10	diphenylethyne	$(3.2 \pm 0.4) \times 10^{-5}$	11–178	A, B

[a] See Experimental Section. [b] At 16.9 °C. [c] At 18.9 °C.

intermediate; a unified mechanism was recently proposed.[16] On inspection of kinetic data for the bromination of alkynes in acetic acid,[17,18] both similarities and differences may be observed. Alkylacetylenes are more reactive toward bromine than aryl ones (e.g., $k_{3\text{-hexyne}}/k_{\text{diphenylethyne}} = 28$[17]), as toward $Hg(OAc)_2$, but the selectivity of the latter reaction is much higher ($k_{4\text{-octyne}}/k_{\text{diphenylethyne}} = 1.6 \times 10^6$). A much lower difference in selectivity was observed with alkenes, although in a different solvent (MeOH), oxymercuration being again more selective than bromination.[19,20]

Considering alkylarylalkynes, an increase in the length of the alkyl chain causes an increase of reactivity in bromination ($k_{PhC\equiv CCH_3}/k_{PhC\equiv CC_2H_5} = 0.4$)[17] and a decrease in acetoxymercuration ($k_{PhC\equiv CCH_3}/k_{PhC\equiv CC_3H_7} = 2.1$). This suggests that steric effects play a more important role in mercuration than in bromination, as already observed for alkenes.[16,20]

A rate decrease with increasing chain length is also observed in the case of dialkylalkynes (Table I, entries 1 and 2), but the effect is quite small and falls within the experimental errors. This might depend on the high reactivity and low selectivity of the substrates with respect to alkylarylalkynes.

Activation parameters were determined for the reaction of 1-phenylpropyne, diphenylethyne, and 1,4-dimethoxy-2-butyne (Table III). The values for aryl derivatives seem to indicate that the difference in reactivity results essentially from difference in activation enthalpy, the activation entropy being the same, within experimental error. Because of the sensitivity of oxymercuration to steric crowding, it is likely that differences in transition rather than in ground states are responsible for the observed results. However, a conclusion cannot be drawn, since thermochemical data are available for diphenylethyne[21] only.

The negative activation entropy is consistent with an associative process. Activation parameters are somewhat different from those reported for the acid-catalyzed hydration of phenylacetylenes[22] but very similar to the values observed for the methoxymercuration of styrene derivatives.[20]

Table II. Experimental Data for a Typical Kinetic Run: Reaction between 1,4-Diacetoxy-2-butyne and $Hg(OAc)_2$ in AcOH at 25.0 °C[a]

A_t	t, s	A_t	t, s
0.210	0	0.772	80
0.315	10	0.810	90
0.420	20	0.840	100
0.500	30	0.865	110
0.576	40	0.888	120
0.640	50	0.903	130
0.690	60	0.916	140
0.730	70	0.930	150

[a] [alkyne] = 1.5×10^{-3}; $[Hg(OAc)_2]$ = 0.020 M; A_∞ = 1.016; k_{obsd} = 0.015 s^{-1}; correlation coefficient = 0.99978; reaction % followed 89; k = 0.75 M^{-1} s^{-1}.

An unsymmetrically bridged cation has been proposed as the intermediate in the oxymercuration of alkyl-substituted styrenes[20] and, more recently, of alkenes in general, on the basis of MNDO calculations.[23]

The similarities in the oxymercuration of alkenes and alkynes may suggest a bridged vinyl cation as the intermediate of the rate-limiting step for the latter compounds also. The fact that the intermediate is probably a bridged species is supported by the relative reactivities of alkyl- and arylalkynes (Table I, entries 1 and 7). If open species were involved, the transition states for acetoxymercuration should reflect to some extent the energy difference of fully developed vinyl cations. However, phenylvinylcations are more stable than alkylvinyl ones by a factor ranging from 25 to 35 kcal/mol.[24]

To better understand the mechanism of alkynes oxymetalation, further investigation is in progress concerning substituent, solvent, and metal effects. A comparison of alkene vs. alkyne reactivity in the same conditions is also under investigation, since it is important for the elucidation of the addition mechanism.[25]

Experimental Section

Gas chromatographic analyses have been carried out with a Hewlett-Packard Model 5830A apparatus equipped with a 0.5-m 2% OV 17 Chromosorb GAW-DMCS column.

^1H NMR spectra have been recorded on a Bruker WP-80 and a Varian EM-360 spectrometer with $CDCl_3$ or CCl_4 as solvents and Me_4Si as the internal standard.

Spectrophotometric measurements have been performed with Cary 219 and Varian DMS 90 spectrophotometers and a Durrum-Gibson 110 stopped-flow spectrophotometer equipped with a Biomation Model 805 recorder.

(16) Fuzukumi, S.; Kochi, J. K. *J. Am. Chem. Soc.* **1981**, *103*, 2783.
(17) Schmid, G. H.; Modro, A.; Yates, K. *J. Org. Chem.*, **1980**, *45*, 665.
(18) Modena, G.; Rivetti, F.; Tonellato, U. *J. Org. Chem.* **1978**, *43*, 1521.
(19) Bamford, C. H.; Tipper, C. H. F., Eds. *Comprehensive Chemical Kinetics*; Elsevier: Amsterdam, **1973**; Vol. 9, and references therein.
(20) Bassetti, M.; Floris, B.; Illuminati, G. *J. Organomet. Chem.* **1980**, *202*, 351.
(21) Pedley, J. B.; Rylance, J. *Sussex-N.P.L. Computer Analysed Thermochemical Data: Organic and Organometallic Compounds*; University of Sussex: Sussex, 1977.
(22) Noyce, D. S.; Schiavelli, M. D. *J. Am. Chem. Soc.* **1968**, *90*, 1020.
(23) Dewar, M. J. S.; Merz, K. M., Jr. *Organometallics*, **1985**, *4*, 1967.
(24) Mayr, M.; Schneider, R.; Wilhelm, D.; Schleyer, P. v. R. *J. Org. Chem.* **1981**, *46*, 5336.
(25) Melloni, G.; Modena, G.; Tonellato, U. *Acc. Chem. Res.* **1981**, *14*, 227.

Table III. Activation Parameters for the Acetoxymercuration of Some Alkynes

alkyne	$\Delta H^{\ddagger}$, kcal/mol	sd[a]	$\Delta S^{\ddagger}$, eu	sd[a]	r^b	range of temp, °C
$CH_3OCH_2C{\equiv}CCH_2OCH_3$	11.0	0.5	-23	1.7	0.997	25.0–59.0
$PhC{\equiv}CCH_3$	11.5	0.4	-33	2	0.999	25.0–59.2
$PhC{\equiv}CPh$	13.9	0.3	-32	0.9	0.999	25.0–89.3

[a] Standard deviation. [b] Correlation coefficient.

Materials. 4-Octyne, diphenylethyne, mercuric acetate, and acetic acid were commercially available reagent grade products and were used without further purification.

1-Phenylpropyne,[26] 1-phenyl-1-pentyne,[27] 2-heptyne, 2-nonyne, methyl 3-phenylpropynoate, methyl 2-octynoate, 1,4-diacetoxy-2-butyne,[28] and 1,4-dimethoxy-2-butyne[29] were prepared according to literature methods or to an appropriate modification. All the synthesized alkynes were purified by distillation and checked for purity by gas chromatography (≥98%).

Product Analysis. Acetoxymercuration products were isolated according to the literature[8,9] by adding mercuric acetate in AcOH to an equivalent amount of the alkyne in the same solvent. After a reaction time ranging between 30 min and 24 h at room temperature, the solvent was removed under vacuum to avoid heating, and the residue was washed with water, extracted with CH_2Cl_2, and dried over anhydrous Na_2SO_4. Evaporation of dichloromethane gave almost quantitative amounts of the adducts.

The products were characterized by ^1H NMR spectrometry. Proton NMR spectra of previously prepared compounds are in agreement with the reported data. For the acetoxymercuration products from the other alkynes, the spectra are as follows.

From 2-heptyne: δ 2.15 and 2.14 (two s, 3 H altogether, $OCOCH_3$), 2.00 (s, 3 H, $HgOCOCH_3$), 2.10 and 1.80 (two s, 3 H altogether, $=C(OAc)CH_3$ and $=C(HgOAc)CH_3$, respectively), 1.4 (complex signal, 4 H, $-CH_2CH_2-$), and 0.9 (complex signal, 3 H, $-CH_2CH_3$). The resonance of $-CH_2C=$ protons occurs around δ 2.3 and in the range δ 2.15–2.00, where it is covered by the methyl groups signals. By integration of selected peaks (δ 1.80 and 0.9, respectively), two regioisomers were recognized, in approximately equal amounts.

From 2-nonyne: δ 2.4 (complex signal, 2 H, $-CH_2C=$), 2.12–2.10 (two s superimposed, 4.5 H in all, $OCOCH_3$ and $=C(OAc)CH_3$), 2.00 (s, 3 H, $HgOCOCH_3$), 1.75 (s, 1.5 H, $=C(HgOAc)CH_3$), 1.3 (broad, 8 H, $-(CH_2)_4-$), and 0.8 (broad, 3 H, $-CH_3$).

Two regioisomers were identified in a ca. 1:1 ratio.

From methyl 3-phenylpropynoate: δ 7.3 (complex signal, 5 H, Ph), 3.76 and 3.66 (two s, 3 H altogether, $=C(OAc)CO_2CH_3$ and $=C(HgOAc)CO_2CH_3$, respectively), 2.24 (s, 3 H, $OCOCH_3$), and 1.98 (s, 3 H, $HgOCOCH_3$). The two regioisomers, $PhC(OAc)=C(HgOAc)CO_2CH_3$ and $PhC(HgOAc)=C(OAc)CO_2CH_3$, are roughly 40% and 60%, respectively.

From methyl 2-octynoate: δ 3.68 (s, 3 H, CO_2CH_3), 2.16 (s, 3 H, $OCOCH_3$), 2.00 (s, 3 H, $HgOCOCH_3$), 1.4 (broad multiplet, 6 H, $-(CH_2)_3-$), and 0.9 (t, 3 H, $-CH_2CH_3$). The resonance of $-CH_2C=$ is a triplet in the range δ 2.3–2.4, partially superimposed to the signal due to the acetoxy groups.

Kinetic Measurements. Kinetic experiments have been carried out under pseudo-first-order conditions, with different methods.

(A) Known quantities in acetic acid of excess $Hg(OAc)_2$, the alkyne, and the appropriate internal standard were mixed in a thermostated reaction vessel. Samples (0.5 mL) of the reaction mixture were taken with a syringe at different times and added to 2 mL of water and 1 mL of CCl_4 in a separatory funnel. The organic phase was examined at the gas chromatograph immediately after separation. Blank experiments were carried out to check the reliability of the method. Octadecane and undecane were used as the internal standard with diphenylethyne and 1-phenylpropyne, respectively. The disappearance of the substrate was followed with time, mercurated species being not detectable by gas chromatography.

(B) Solutions at known concentrations of the reactants were separately put in a silica cell with septum, thermostated in the cell compartment of the spectrophotometer, and mixed. The absorbance increase due to the formation of the product was followed with time, between 260 and 310 nm. When infinity time absorbance was not available, due to the occurrence of subsequent reactions, the value was extrapolated according to the Mangelsdorf's method.[30]

(C) The kinetics of fast reacting substrates were followed by the stopped-flow technique.

The data are reported in Table I as overall second-order constants. They are mean values of several runs carried out under conditions specified as follows (temperature, wavelengths, and fraction of the reaction followed are given in parentheses).

4-Octyne. $C_3H_7C{\equiv}CC_3H_7$, 7.2×10^{-4}–7.0×10^{-3} M; $Hg(OAc)_2$, 8.1×10^{-3}–7.8×10^{-2} M (25.0, 16.9, and 18.9 °C, 285 and 288 nm, ≥90%).

2-Heptyne. $CH_3(CH_2)_3C{\equiv}CCH_3$, 4.0×10^{-4} M; $Hg(OAc)_2$, 4.0×10^{-3} M (16.9 °C, 280 nm, 80%).

2-Nonyne. $CH_3(CH_2)_5C{\equiv}CCH_3$, 3.9×10^{-4} M; $Hg(OAc)_2$, 4.0×10^{-3} M (16.9 °C, 290 nm, 70–80%).

1,4-Dimethoxy-2-butyne. $CH_3OCH_2C{\equiv}CCH_2OCH_3$, 1.4×10^{-3}–3.5×10^{-3} M; $Hg(OAc)_2$, 1.6×10^{-2}–4.1×10^{-2} M (25.0 °C, 290 nm, 50–60%).

1,4-Diacetoxy-2-butyne. $AcOCH_2C{\equiv}CCH_2OAc$, 3.0×10^{-4}–1.5×10^{-3} M; $Hg(OAc)_2$, 5.0×10^{-3}–2.0×10^{-2} M (25.0 °C, 290 nm, 80–90%).

Methyl 2-Octynoate. $C_5H_{11}C{\equiv}CCO_2CH_3$, 2.6×10^{-3} M; $Hg(OAc)_2$, 6.2×10^{-2}–7.8×10^{-2} M (25.0 °C, 290 nm, 60–70%).

1-Phenylpropyne. $PhC{\equiv}CCH_3$, 4.4×10^{-5}–5.8×10^{-3} M; $Hg(OAc)_2$, 5.5×10^{-4}–9.0×10^{-2} M (25.0 °C, 280, 286, and 290 nm, 65–80%).

1-Phenyl-1-pentyne. $PhC{\equiv}CC_3H_7$, 3.8×10^{-4} M; $Hg(OAc)_2$, 4.7×10^{-2}–5.0×10^{-2} M (25.0 °C, 289 nm, 80%).

Methyl 3-phenylpropynoate. $PhC{\equiv}CCO_2CH_3$, 3.0×10^{-5}–3.2×10^{-5} M; $Hg(OAc)_2$, 7.8×10^{-2}–9.3×10^{-2} M (25.0 °C, 310 nm, 50%).

Diphenylethyne. $PhC{\equiv}CPh$, 4.5×10^{-4}–1.3×10^{-2} M; $Hg(OAc)_2$, 7.8×10^{-2}–0.15 M (25.0 °C, 310 nm, 60–80%).

Values for a typical run are given in Table II.

Activation Parameters. The rate measurements at various temperatures were duplicated. Evaluation of the observed rate constants is critical at temperatures higher than 50 °C, because of the interference from further reactions of acetoxymercury vinyl derivatives.[8,13] Good Arrhenius plots were obtained in all cases. The related data, in addition to the rate coefficients in Table I, are as follows (temperature is given in parentheses).

1-Phenylpropyne. $PhC{\equiv}CCH_3$, 1.7×10^{-4}–8.0×10^{-4} M; $Hg(OAc)_2$, 4.2×10^{-4}–4.0×10^{-2} M; k_2 (M^{-1} s^{-1}) = 4.4×10^{-3} (33.4 °C), 5.5×10^{-3} (40.0 °C), 8.1×10^{-3} (44.8 °C), 1.5×10^{-2} (56.3 °C).

Diphenylethyne. $PhC{\equiv}CPh$, 5.0×10^{-3}–1.0×10^{-2} M; $Hg(OAc)_2$, 0.093–0.15 M; k_2 (M^{-1} s^{-1}) = 3.1×10^{-4} (53.4 °C), 7.7×10^{-4} (68.1 °C), 2.5×10^{-3} (89.3 °C).

1,2-Dimethoxy-2-butyne. $CH_3OCH_2C{\equiv}CCH_2OCH_3$, 3.5×10^{-4}–3.5×10^{-3} M; $Hg(OAc)_2$, 4.05×10^{-3}–4.1×10^{-2} M; k_2 (M^{-1} s^{-1}) = 0.84 (37.1 °C), 1.8 (47.8 °C), 3.2 (59.0 °C).

The results are reported in Table III.

Acknowledgment. Partial financial support from the Ministero della Pubblica Istruzione is acknowledged.

Registry No. $C_3H_7C{\equiv}CC_3H_7$, 1942-45-6; $CH_3(CH_2)_3C{\equiv}CCH_3$, 1119-65-9; $CH_3(CH_2)_5C{\equiv}CCH_3$, 19447-29-1; $CH_3OCH_2C{\equiv}CCH_2OCH_3$, 16356-02-8; $AcOCH_2C{\equiv}CCH_3OAc$, 1573-17-7; C_5H_{11}-

(26) Dewar, M. J. S.; Fahey, R. C. *J. Am. Chem. Soc.* **1963**, *85*, 3645.
(27) Johnson, J. R.; Schwartz, A. M.; Jacobs, Th. L. *J. Am. Chem. Soc.* **1938**, *60*, 1882.
(28) Levina, R. Ya.; Shabarov, Yu. S. *Vestn. Mosk. Univ., Ser. Fiz.-Mat. Estest. Nauk* **1956**, *4*, 61; *Chem. Abstr.* **1957**, *51*, 7299.
(29) Hennion, G. F.; Kupiecki, F. P. *J. Org. Chem.* **1953**, *18*, 1601.
(30) Bamford, C. H.; Tipper, C. F. H. *Comprehensive Chemical Kinetics*; Elsevier: Amsterdam, 1969, Vol. 1.

$C{\equiv}CCO_2CH_3$, 111-12-6; $PhC{\equiv}CCH_3$, 673-32-5; $PhC{\equiv}CC_3H_7$, 4250-81-1; $PhC{\equiv}CCO_2CH_3$, 4891-38-7; PhC≡CPh, 501-65-5; $Hg(OAc)_2$, 1600-27-7; $CH_3C(OAc){=}C(HgOAc)(CH_2)_3CH_3$, 104114-79-6; $CH_3C(HgOAc){=}C(OAc)(CH_2)_3CH_3$, 104114-80-9; $CH_3C(OAc){=}C(HgOAc)(CH_2)_5CH_3$, 104114-81-0; $CH_3C(HgOAc){=}C(OAc)(CH_2)_5CH_3$, 104114-82-1; $PhC(OAc){=}C(HgOAc)CO_2CH_3$, 104114-83-2; $PhC(HgOAc){=}C(OAc)CO_2CH_3$, 104114-84-3.

Supplementary Material Available: Kinetic data and graphs of kinetic runs of 1,4-diacetoxy-2-butyne with mercuric acetate in acetic acid at 25 °C and 1-phenyl-1-pentyne with mercuric acetate in acetic acid at 25 °C (6 pages). Ordering information is given on any current masthead page.

α-D-Ribofuranosyl 1,2-Cyclic Monophosphate. Isolation, NMR Spectroscopic Properties, and Rates and Mechanism of Acid and Alkaline Hydrolysis

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Received April 3, 1986

The five-membered ring cyclic phosphate α-D-ribofuranosyl 1,2-cyclic phosphate has been synthesized, isolated, and characterized both spectroscopically and with respect to acid and alkaline lability. The ^{31}P NMR chemical shift (17 ppm downfield from internal HPO_4^{2-} at pH 8.0) is similar to that observed for 2′,3′-cAMP and considerably deshielded compared to that of the glucopyranosyl analogue (8.0 ppm). Alkaline hydrolysis of α-D-ribofuranosyl 1,2-cyclic phosphate and of α-D-glucopyranosyl 1,2-cyclic phosphate under identical conditions proceeded at very similar rates and in the former was demonstrated to result in hydroxide attack at the P atom (by employing a specifically ^{18}O-labeled substrate) and led to the formation of both sugar 1- and 2-phosphates. The fast rates of alkaline hydrolysis were similar to those reported for ethylene phosphate (Kumamoto, J.; Cox, J. R.; Westheimer, F. H. *J. Am. Chem. Soc.* **1956**, *78*, 3423), presumably due to the presence of a strained cyclic phosphate ring. Acid hydrolysis of α-D-ribofuranosyl 1,2-cyclic phosphate led to the exclusive formation of the ribose 2-phosphates, presumably by the scission of the anomeric C–O bond.

Two cyclic monophosphate esters of ribofuranose have been found to possess important biological function: the 3′,5′-monophosphates of nucleosides are second hormonal messengers,[1] the 2′,3′-monophosphates of nucleosides are intermediates in the ribonuclease-catalyzed reactions of ribonucleic acids.[2a,b] Although the synthesis of another class, the α-D-ribofuranosyl 1,2-cyclic phosphate was reported by Khorana and associates,[3] no purification, isolation, or spectral or chemical properties were reported. The well-documented behavior of the parent compound ethylene phosphate suggests that such five-membered ring phosphate esters may be both kinetically[4] and thermodynamically[5] unstable to hydrolysis compared to their acyclic analogues. Our interest in the 1,2-cyclic phosphates of ribose stems from the fact that enzymes on the purine salvage pathway employ as substrates α-D-ribofuranosyl 1-phosphate and 5-phospho-α-D-ribofuranosyl-1-pyrophosphate in phosphate (PO_4) and pyrophosphate transfer, respectively, and the related 1,2-cyclic phosphates may act as electrophilic traps for nucleophiles on these enzymes. In fact, we have preliminary evidence that indicates irreversible inhibition of purine nucleoside phosphorylase (EC 2.4.2.1) by α-D-ribofuranosyl 1,2-cyclic monophosphate.[6] Here we report improved synthesis, NMR spectroscopic properties and rates and mechanism of specific acid and base-catalyzed hydrolyses of this compound. In both its spectroscopic properties and alkaline hydrolytic lability the title compound resembles the 2,3-isomer.

Table I. Ascending Paper[a] Chromatography of Relevant Compounds

compound	solvent A[b]	solvent B[c]
α-D-ribofuranosyl 1-phosphate	0.05	0.33
α-D-ribofuranosyl 1,2-cyclic phosphate	0.56	0.73
α-D-glucopyranosyl 1-phosphate	0.09	0.28
α-D-glucopyranosyl 1,2-cyclic phosphate	0.38	0.65

[a] Whatman No. 31 E/T (0.53 mm, fast flow rate). [b] Isopropyl alcohol/NH_3/H_2O (7:1:2 v/v). [c] *n*-Propyl alcohol/NH_3/H_2O (6:1:3 v/v).

Table II. ^{31}P NMR Chemical Shifts of Cyclic Phosphates

compound	δ
α-D-ribofuranosyl 1,2-cyclic phosphate	17.0
5-phospho-α-D-ribofuranosyl 1,2-cyclic phosphate[b]	17.0
α-D-glucopyranosyl 1,2-cyclic phosphate	8.2
6-phospho-α-D-glucopyranosyl 1,2-cyclic phosphate[b]	8.0
2′,3′-cyclic AMP	17.5
3′,5′-cyclic AMP	−4.0

[a] Measured at 25 °C, pH 8.0, in the presence of 10 mM EGTA; positive sign represents downfield and a negative sign upfield from internal HPO_4^{2-}. [b] Synthesis and properties to be published.

Results and Discussion

Isolation and Purification of α-D-Ribofuranosyl 1,2-Cyclic Phosphate (1) and α-D-Glucopyranosyl 1,2-Cyclic Phosphate (2). The synthetic protocol enabled us to isolate larger amounts of 1, which then could be

(1) Rall, T. W., Sutherland, E. W. *J. Biol. Chem.* **1958**, *232*, 1065.
(2) (a) Brown, D. M.; Todd, A. R. *J. Chem. Soc.* **1952**, 52. (b) Brown, D. M.; Magrath, D. J.; Todd, A. R. *J. Chem. Soc.* **1952**, 2708.
(3) Wright, R. S.; Khorana, H. G. *J. Am. Chem. Soc.* **1955**, *77*, 3423.
(4) Kumamoto, J.; Cox, J. R., Jr.; Westheimer, F. H. *J. Am. Chem. Soc.* **1956**, *78*, 4858.
(5) Sturtevant, J. M.; Gerlt, J. A.; Westheimer, F. H. *J. Am. Chem. Soc.* **1973**, *95*, 8168.
(6) Jordan, F.; Fathi, R. *Phosphorus Sulfur*, **1983**, *18*, 341.

0022-3263/86/1951-4143$01.50/0